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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/974,546	10/10/2001	Gang An	UROC:018USD2	8133

7590 11/22/2004

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 11/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/974,546	AN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2004 and 20 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *78-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20020122*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The supplemental election of the species of invention filed August 16, 2004 is acknowledged and has been entered. Applicant has elected the species of invention wherein said cancer is prostate cancer. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of a species of invention has been treated as an election without traverse (MPEP § 818.03(a)).

2. The election of invention with traverse filed April 20, 2004 is acknowledged and has been entered. Applicant has elected the invention of Group XIX, claims 78-94, drawn to a method for treating cancer comprising administering an agent that inhibits a peptide or polypeptide encoded by SEQ ID NO: 83 or a fragment thereof.

3. Claims 78-94 are pending in the application and are currently under prosecution.

Election/Restrictions

4. Applicant's traversal of the restriction and election requirement set forth in the Office action mailed October 21, 2003 is acknowledged. Applicant has argued the requirement is improper because the inventions of Groups XIX and XX are both drawn to a method for treating cancer comprising administering an inhibitor of the same protein, since the nucleic acid molecules comprising SEQ ID NO: 83 and SEQ ID NO: 85 are disclosed as encoding a polypeptide comprising the same amino acid sequence.

Applicant's argument has been favorably considered. The inventions of Groups XIX and XX have therefore been rejoined.

Furthermore, after further consideration of the requirement, the requirement to elect a species of invention by selecting one of the three types of cancer listed in claim 85 is withdrawn.

Information Disclosure Statement

5. The information disclosure filed December 17, 2001 has been considered. An initialed copy is enclosed.

Priority

6. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Although the instant application contains a statement referencing prior nonprovisional US Application No. 09/662,270, the statement lacks an indication of the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications.

It is further noted that the statement should include an indication of the present status of the referenced applications (i.e., an indication of whether the application referred to is now abandoned or issued as a US Patent). US Application No. 09/662,270 is now abandoned; and US Application No. 08/692,787 issued as US Patent No. 5,882,864 on March 16, 1999.

Specification

7. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an

unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the sequence "GLECCL", which is depicted at page 117, line 24, is not identified.

Applicant must provide an appropriate amendment to the specification, inserting the required sequence identifier.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with a statement that the content of both copies are the same and, where applicable, include no new matter.

8. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such improperly demarcated trademarks include: MacVector™ (page 31, line 21); Tween™ (page 51, line 27); and GeneClean™ (page 87, line 17).

Appropriate corrections are required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

9. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code

and to the Internet contents so identified is impermissible and therefore requires deletion.

An example of such an impermissible reference appears in the specification at page 119, lines 8 and 9.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference.

Claim Objections

10. Claims 78-94 are objected to because the claims are drawn in the alternative to the subject matter of non-elected inventions. Appropriate correction is required.

11. Claims 83 and 92 are objected to because "radionuclide" is misspelled as "radionucleotide". Appropriate correction is required.

12. Claim 86 is objected to because the claim is drawn to the method of claim 78, wherein the agent inhibits SEQ ID NO: 83 or a fragment thereof, or SEQ ID NO: 85 or a fragment thereof. SEQ ID NO: 83 and SEQ ID NO: 85 are polynucleotide sequences. Claim 78 is drawn to a method for treating cancer comprising administering an inhibitor of **a polypeptide encoded by** SEQ ID NO: 83 or a fragment thereof, or SEQ ID NO: 85 or a fragment thereof, not an inhibitor of a polynucleotide. This issue can be remedied by amending claim 86 to recite, for example, "wherein the agent inhibits the polypeptide encoded by SEQ ID NO: 83 or a fragment thereof, or the polypeptide encoded by SEQ ID NO: 85 or a fragment thereof". Appropriate correction is required.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 78-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 78-94 are drawn to a method for treating cancer comprising administering a member of a genus of "inhibitors" of a peptide or polypeptide.

The subject matter of the claims is not described in a manner that would reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed, since, in particular, the specification does not include a description of an activity or function of the polypeptide encoded by the nucleic acid molecules of SEQ ID NO: 83 and SEQ ID NO: 85, which can be inhibited, and accordingly, it also fails to describe an inhibitor of such a peptide or polypeptide, which can be administered to a patient to treat cancer in the patient.

The specification describes the polynucleotides of SEQ ID NO: 83 and SEQ ID NO: 85 as novel (page 111, Table 3). While disclosing that both polynucleotides encode the same protein (page 115, lines 11-15), the specification does not describe a function or activity of this protein, and apart from disclosing some results of a preliminary analysis of the amino acid sequence (page 117, lines 19-27), merely describes the protein as localized on the cell membrane of epithelial cells (page 117, lines 10-14).

The description of the claimed invention would therefore not be sufficiently detailed to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed, because the skilled artisan could not immediately envision, recognize, or distinguish an inhibitor suitable for use in practicing the claimed invention.

For example, while the inhibitor could be a monoclonal antibody that binds the protein, because the activity or function of the protein has not been described, an

antibody that binds to the protein and thereby inhibits its activity or function cannot be immediately envisioned, recognized, or distinguished, given only the description of the claimed invention set forth in the specification. An antibody that binds the polypeptide may not inhibit its function, as the antibody may be agonist or otherwise, the antibody may not affect the activity of the polypeptide. Consequently, the skilled artisan cannot envision an inhibitor of an activity or function that has not been described, nor could the skilled artisan distinguish a compound capable of inhibiting the activity or function in the absence of such a description. The specification does not reasonably convey Applicant's possession of the claimed invention, due to the lack of an adequate written description of the function that is inhibited by the members of the genus of "inhibitors" that are administered to the patient.

In point of fact, the specification discloses that inhibitors of the protein encoded by the newly identified polynucleotides of SEQ ID NO: 83 and SEQ ID NO: 85 "could [...] potentially be designed" (page 74, lines 3 and 4); however, the specification discloses that doing this would be "complicated by the fact that no specific function has been identified for [...] these gene products, and no data is available on their three-dimensional structures" (page 74, lines 4-6). Because a specific function or activity of the protein encoded by the polynucleotides of SEQ ID NO: 83 and SEQ ID NO: 85 has not been described, the skilled artisan could not envision, recognize, or distinguish an inhibitor of the protein, and therefore the instant disclosure of the claimed invention cannot be considered sufficient to meet the written description requirement set forth under 35 USC § 112, first paragraph.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104).

The members of the genus of inhibitors of the polypeptide encoded by SEQ ID NO: 83 and SEQ ID NO: 85 are expected to vary markedly in both structure and function (i.e., mode of action), depending upon the function of the polypeptide that is inhibited. The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106). It follows that an adequate written description of a genus cannot be achieved *in the absence of a disclosure of at least one* species within the genus.

Because the claims are directed to the use of a genus of variant species of inhibitor, an adequate written description of the claimed invention must include sufficient description of at least a representative number of different species of inhibitor by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. Factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed. Accordingly, the disclosure of the claimed invention fails to meet the written description requirement set forth under 35 USC § 112, first paragraph.

15. Claims 78-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 78-94 are drawn to a method for treating cancer cells in a patient comprising administering to the patient an inhibitor of the polypeptide encoded by SEQ ID NO: 83 or SEQ ID NO: 85, including an antibody that binds the polypeptide.

The amount of guidance, direction, and exemplification set forth in the specification would not be sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The specification teaches SEQ ID NO: 3 is the polynucleotide sequence of an expressed sequence tag (EST), which is abundantly expressed, compared to normal, in prostate, breast, and bladder cancer; see, e.g., Figures 3, 15, and 16. The specification teaches that the polynucleotide of SEQ ID NO: 3 was used as a probe to select the full-length complementary DNA (cDNA) molecules of SEQ ID NO: 83 and SEQ ID NO: 85, which were derived from two alternatively spliced messenger RNA (mRNA) variants encoding the same protein having the amino acid sequence set forth as SEQ ID NO: 84 and SEQ ID NO: 86 (page 115, lines 6-15).

The specification teaches these isolated polynucleotides and the polypeptide encoded by the polynucleotides were not previously known or described (page 111, Table 3). The specification does not teach what function or biologic activity the polypeptide has; yet, the claimed invention is a method for treating cancer, which comprises administering to a patient an inhibitor of the polypeptide. Because the function or activity of the polypeptide is not disclosed, the skilled artisan could not use the claimed invention without first having to perform an undue amount of additional experimentation to first determine the function or activity of the protein, secondly to determine whether the function or activity of the protein correlates with the onset or progression of cancer, and if so, then to design or discover a compound that inhibits that function or activity, which can be used in practicing the claimed invention to treat cancer.

The specification discloses, "identification of protein function can be extrapolated, in some cases, from primary sequence data, provided that sequence homology exists between the unknown protein and a protein of similar sequence and known function" (page 71, lines 7-9). However, the specification does not teach whether the polypeptide encoded by the polynucleotide sequences of SEQ ID NO: 83 and SEQ ID NO: 85 is homologous to proteins having known functions; and nevertheless, Skolnick et al. (*Trends in Biotechnology* **18**: 34-39, 2000), for example, discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part, because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Skolnick et al. teaches that even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Thus, contrary to the assertions set forth in the instant disclosure, the skilled artisan cannot reliably and accurately predict the function of a novel protein upon the basis of only an observed similarity in its amino acid sequence and those of other proteins having known functions.

Even if the function or activity of the polypeptide were known, the skilled artisan could still not use the claimed invention without first having to perform an undue amount of additional experimentation, because the specification does not teach the skilled artisan to make an inhibitor of the polypeptide, which, in particular, can be used in practicing the claimed invention to treat cancer. Additionally, even though cancer cells may overexpress the protein, its function or activity may not be associated with the onset or progression of cancer; therefore, an inhibitor of the polypeptide may not inhibit the onset or progression of cancer in the patient and would therefore not provide an effective treatment of cancer. Consequently, before designing or striving to discover an inhibitor of the protein, the skilled artisan would have to determine if such an inhibitor might be therapeutically valuable.

Even if the activity of the protein were known to be associated with the onset or progression of cancer, the art of anticancer drug discovery is unfortunately hindered by the extreme complexity of the biological system and its inherently unpredictable nature and consequently an inhibitor of the polypeptide could not be made by routine experimentation alone. For example, Gura (*Science* **278**: 1041-1042, 1997) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Because of the lack of predictability in the art, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, indicating that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2).

Furthermore, because of the refractory nature of cancer to drugs, the design and discovery of effective drugs can be, and usually is, daunting. Jain (*Scientific American* **271**: 58-65, 1994), for example, teaches that most tumors resist full penetration by anticancer agents (page 58, column 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (page 65, column 3). Curti (*Critical Reviews in Oncology/Hematology* **14**: 29-39, 1993) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited. Curti discloses that our knowledge about the physical barriers to drug delivery in tumors is a work in progress (page 36, column 2). Curti teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and, if this is true, designing effective

chemotherapeutic regimens for solid tumors may prove a burdensome task (paragraph bridging pages 29-30).

Anti-tumor agents must accomplish several tasks to be effective. The agents must be delivered into the circulation that supplies the tumor and interact at the proper site, and they must do so at a sufficient concentration and for a sufficient period of time so as to be effective. Also, the targeted cells must not have an alternate means of survival despite action at the proper site for the drug. In addition, variables such as biological stability, half-life, and clearance from the blood are important parameters in achieving successful therapy. The composition may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation, or due to an inherently short half-life. The composition may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted. Alternatively, the composition may be absorbed by fluids, cells and tissues where the formulation has no effect and circulation into the target area may be insufficient to carry the composition and to permit a large enough local concentration to be established.

It is noted that the claims specifically encompass a method for treating cancer, which comprises administering to a patient an antibody that binds the polypeptide; however, while the specification teaches the protein has been localized to epithelial cells, "mainly on the cell membrane" (page 117, lines 10-14), the specification does not actually teach whether the protein is expressed at the surface of the cells. If the inhibitor is an antibody or another type of inhibitor that binds directly to the polypeptide, and the polypeptide is not expressed at the surface of the targeted cancer cells, the antibody or other inhibitor cannot specifically bind those cells and therefore will have no specific inhibitory effect upon those cells. Accordingly, an undue amount of additional experimentation would be necessary to determine if the protein is expressed at the surface of cancer cells before the skilled artisan could use the claimed invention to treat cancer in a patient.

In this regard, it appears that An et al. (*Cancer Research* **60**: 7014-7020, 2000) teaches the gene encoding the protein, which is designated therein as UROC28, is not expressed at the surface of cells, since immunohistochemical analyses of glandular

epithelial cells of prostate and breast cancers revealed the protein localizes in the nucleus and cytoplasm; see entire document, particularly page 7018, Figure 5. Furthermore, An et al. discloses the presence of the protein in human serum specimens acquired from patients diagnosed with prostate cancer (see, e.g., page 7018, figure 6). All together, An et al. suggests that, rather than expressed at the surface of cells of epithelial origin, the protein is either nuclear or cytoplasmic, or both, and can be secreted. Again, if the protein is not expressed at the surface of targeted cancer cells, however, an antibody or other inhibitor that binds directly to the protein cannot be used, because the antibody or other inhibitor cannot bind a protein that is expressed within the cell, and if the protein is secreted, while the antibody or inhibitor could bind the protein, its binding to the protein will not affect the cancer cells that secreted the protein.

Even if the protein were expressed at the surface of the targeted cancer cells, and the inhibitor is an antibody that binds the protein, it is aptly noted that, while antibody-targeted therapy can overcome some of the intrinsic shortcomings that reduce the efficacy of agents that are non-selective or non-tumor-specific, there are well known limitations in the art of antibody-targeted therapeutic regimens. Vitetta et al. (*Cancer Research* **54**: 5301-5309, 1994) (of record) teaches: "[D]espite [...] intellectual appeal, the general therapeutic efficacy of tumor-reactive MAbs [monoclonal antibodies] has been disappointing. In particular the results of clinical studies in patients with solid tumors showed little efficacy, except in the setting of minimal disease" (citations omitted) (page 5301, column 1). Vitetta et al. teaches that there are a number of significant limitations in their use as first-line therapy for solid tumors page 5305, (columns 1-2):

> Only 0.001 to 0.1% of injected MAb [monoclonal antibody] will localize to each [gram] of tumor mass. Moreover, MAbs, even at high serum concentrations, cannot gain access to all the cells in solid epithelial tumor. The reasons for this are poor and heterogeneous blood supply, the blood-tumor barrier, and the selective binding of the MAb by the tumor cells closest to the blood supply. In addition, MAbs by themselves probably cannot kill the 10^{10}-10^{12} malignant cells that may be necessary to cure a patient with a disseminated tumor (citations omitted) (page 5305, columns 1-2).

The strategic approach to treating cancer using antibody therapy is analogous to active specific immunotherapy (e.g., vaccination against tumor-associated antigens), at

least to the extent that the latter theoretically induces a humoral immune response (i.e., the production of tumor-specific antibody). Antibody therapy can be defined as passive immunization, cancer vaccine therapy as active immunization. Because the efficacy of both approaches depends upon the effectiveness of tumor antigen-specific antibodies to ameliorate or inhibit tumors, both also share the same or corresponding limitations. Bodey et al. (*Anticancer Research* **20**: 2665-2676, 2000) (of record) teaches:

> Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

Accordingly, as noted above, if a cancer cell does not express the protein that is specifically bound by the antibody at its surface, the use of a pharmaceutical composition comprising such an antibody will not be effective; but, in addition, as Bodey et al. teaches, the use of such a pharmaceutical composition may paradoxically serve to select against tumor cells that express the protein, while promoting the growth of tumor cells that do not express the protein.

It is further noted that the specification does not actually teach that the polypeptide of SEQ ID NO: 84 and SEQ ID NO: 86, which is expressed by the polynucleotides of SEQ ID NO: 83 or SEQ ID NO: 85, is over-expressed in cancer cells, compared to normal cells of the same tissue type. Moreover, the specification fails to demonstrate a correlation between the level of mRNA expression and the level of protein expression in cancer cells. One cannot presume that the amount of protein produced in a cell will mirror the amount of mRNA produced, since Chen et al. (*Molecular & Cellular Proteomics* **1**: 304-313, 2002), for example, teaches that the expression levels protein and mRNA in cancer cells are discordant; see entire

document (e.g., the abstract). Moreover, Lewin has written: "But having acknowledged that control of gene expression can occur at multiple stages, *and that production of RNA cannot inevitably be equated with production of protein*, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription" (italicized for emphasis) (Genes VI, 1997; Ed. Benjamin Lewin; Chapter 29, first page). If the protein is expressed at the surface of cells, and the inhibitor is an antibody, unless the cancer cells, relative to normal cells of the same tissue type, more abundantly express the protein, the antibody will not selectively target cancer cells, but will also undesirably target normal cells. One skilled in the art could therefore not use the claimed invention without first performing an undue amount of additional experimentation to determine if the protein encoded by the polynucleotides of SEQ ID NO: 83 and SEQ ID NO: 85 is over-expressed in prostate, breast, and bladder cancer cells, compared to normal cells of the same tissue type.

Finally, while the claims are drawn to a method for treating any type of cancer, the specification teaches that the polynucleotides of SEQ ID NO: 83 and SEQ ID NO: 85 are not abnormally expressed in colon or lung cancer; see, e.g., Figure 15. Thus, the specification shows that the skilled artisan cannot predict which types of cancer will express the protein, or to what extent; so an undue amount of additional experimentation would have to be performed to characterize the expression of the polypeptide by other types of cancer before the claimed invention could be used to treat cancer in a patient.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation.

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 78-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 78-94 are indefinite because claims 78 and 87 recite the phrase "effective amount". The phrase "effective amount" is indefinite when the claims fail to state the function that is to be achieved. See *In re Frederiksen & Nielsen*, 213 F 2d 547, 102 USPQ 35 (CCPA 1954). In this instance, it cannot be determined if the claim requires the "effective amount" of said agent to be sufficient to effectively inhibit the peptide or polypeptide, or to effectively treat cancer in the patient, or both. Notably, it is entirely possible that an amount of an agent can effectively inhibit an activity of protein, but be insufficient to inhibit the growth of tumor cells. Therefore, the claims would not reasonably apprise the skilled artisan of the metes and bounds of the subject matter that Applicant regards as the invention.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 78-94 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-38 and 65-72 of copending Application No. 09/966,762. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The instant claims are drawn to a method for treating cancer cells comprising administering an inhibitor of a peptide or polypeptide encoded by SEQ ID NO: 83 or SEQ ID NO: 85, which the instant specification discloses is a polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 84 and SEQ ID NO: 86.

Claims 1-38 and 65-72 of the copending application are drawn to a method for inhibiting cancer cells in a patient comprising administering to the patient a "UC28 inhibitor", including a polyclonal or monoclonal antibody that binds "UC28".

SEQ ID NO: 84 of the instant application is identical to SEQ ID NO: 2 of the copending application. The protein comprising this amino acid sequence is designated "UC28" by both the instant and copending applications; see, e.g., page 12, lines 24-27 of the copending application; and page 19, line 4, and page 115, lines 11-15 of the instant application.

The claims of the copending application do not explicitly recite that the antibody administered is conjugated or linked to a radionuclide or chemotherapeutic agent; however, the claims of the copending application do explicitly recite that the antibody can be conjugated to a "toxin", which is defined as either a chemotherapeutic agent or a radionuclide (page 89, lines 2 and 3).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
November 1, 2004

Notice to Comply	Application No.	Applicant(s)	
	09/974,546	AN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: If necessary to correct the deficiency, Applicant must provide substitute sequence listings, together with the statement, as indicated below.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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